

PATENTS SUMMARY

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Index#: 4609

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Assignee: Hisamitsu Pharmaceutical Co. Date of Application: 10/29/92

Title:

CYCLOHEXANOL DERIVATIVE, AGENT AND COMPOSITION CONTAINING THE SAME FOR IMPARTING PLEASANTLY COOL FEELING, PROCESS AND INTERMEDIATE FOR PRODUCING THE DERIVATIVE

Desc.:

A physiological cooling composition containing a cyclohexanol derivative and the method of manufacturing the derivative are claimed. The derivative is 2-(2-alkoxy-1-methyl ethyl)-5-methylcyclohexanol. The compound has several stereoisomers that have strong cooling action and almost no odor. Isopregol is the starting material. It is used in cosmetics and medications for oral and topical use. Use in chewing gum is mentioned.

Key Words:

10 CHEWING GUM
414 Menthol
430 Enhancers/Modifiers/Potentiators
459 Cooling Agents
491 Chemicals
525 Chemical Synthesis/Preparation
561 Crystalization
562 Low Toxicity
578 Trigeminal effects
600 ORAL HEALTH
799 Other Company/Institution
810 Patent Cooperation Treaty (PCT)
559 Solubility
560 Reduced Cost/Energy Consumption

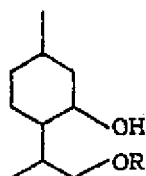


特許協力条約に基づいて公開された国際出願

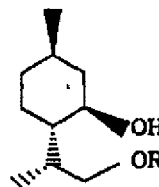
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(21) 国際出願番号 POT/JP93/01562 (22) 国際出願日 1993年10月28日(28. 10. 93) (30) 優先権データ 特願平4/316438 1992年10月29日(29. 10. 92) JP (71) 出願人(米国を除くすべての指定国について) 久光製薬株式会社 (HISAMITSU PHARMACEUTICAL CO., INC.) [JP/JP] 〒841 佐賀県鳥栖市田代大宮町408番地 Saga, (JP) (72) 発明者; および (75) 発明者/出願人(米国についてのみ) 中川 晃 (NAKAGAWA, Akira) [JP/JP] 平野宗彦 (HIRANO, Munehiko) [JP/JP] 小田英志 (ODA, Hideshi) [JP/JP] 栗林 満 (KURIBAYASHI, Mitsuru) [JP/JP] 田上義洋 (TANOUE, Yoshihiro) [JP/JP] 〒841 佐賀県鳥栖市田代大宮町408番地 久光製薬株式会社内 Saga, (JP) (74) 代理人 弁理士 伊東辰雄, 外 (ITO, Tatsuo et al.) 〒105 東京都港区虎ノ門二丁目8番1号 虎ノ門電気ビル Tokyo, (JP)	(81) 指定国 AU, CA, JP, KR, US, 欧州特許 (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). 添付公開書類 国際調査報告書 5-80	

(54) Title : CYCLOHEXANOL DERIVATIVE, AGENT AND COMPOSITION CONTAINING THE SAME FOR IMPART-
 ING PLEASANTLY COOL FEELING, PROCESS FOR PRODUCING THE DERIVATIVE, AND INTERME-
 DIATE THEREFOR

(54) 発明の名称 シクロヘキサノール誘導体、これを含む冷感剤および冷感性組成物、並びに該誘導体の製造方法およびその中間体



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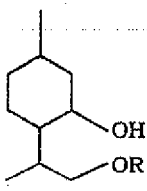
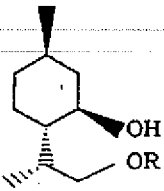


(1a)

(57) Abstract

A cyclohexanol derivative represented by general formula (1), preferably by general formula (1a) (wherein R represents C₁-C₅ linear or branched alkyl). It can impart a sufficient, pleasantly cool feeling to not only the oral mucous membrane but also the skin and is odorless. Further it can provide nearly odorless agent and various compositions for imparting a pleasantly cool feeling.

International Application Published Under the Patent Cooperation Treaty (PCT)

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[21] International File Number: [22] International Application Date: [30] Priority Dates: 1992/316438 <u>Oct. 29, 1992</u> JP [71] Applicants (for all contract countries except US): <u>Hisamitsu Pharmaceutical Co., Inc. (JP/JP)</u> [72] Inventor; and [75] Inventor/Applicant (only for US): Nakagawa, Akira (JP/JP) Hirano, Munchiko (JP/JP) Oda, Hideshi (JP/JP) Kuribayashi, Mitsuru (JP/JP) Tanoue, Yoshihiro (JP/JP) c/o Hisamitsu Pharmaceutical Co., Inc. 408, Tashiro-Daikancho, Tosu-shi, Saga-ken 841 [74] Agent Itoh, Tatsuo et al. Toranomon Denki Bldg., 2-8-1 Toranomon, Minato-ku, Tokyo-to 105		[81] Contract Countries: AU, CA, JP, KR, US, European Patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE) Appended Publications With international search report
[54] Title: <p style="text-align: center;">CYCLOHEXANOL DERIVATIVE, AGENT AND COMPOSITION CONTAINING THE SAME FOR IMPARTING PLEASANTLY COOL FEELING, PROCESS AND INTERMEDIATE FOR PRODUCING THE DERIVATIVE</p> [57] Abstract: <p>A cyclohexanol derivative represented by general formula (1), preferably by general formula (1a) (wherein R represents a C₁-C₃ linear or branched alkyl). It can impart a sufficient, pleasantly cool feeling to not only the oral mucous membrane but also the skin and is odorless. Further, it can provide a nearly odorless agent and various compositions for imparting a pleasantly cool sensation.</p> <div style="display: flex; justify-content: space-around; align-items: center; margin-top: 20px;"> <div style="text-align: center;">  <p>(1)</p> </div> <div style="text-align: center;">  <p>(1a)</p> </div> </div>		

For Information Only

Codes used to identify PCT signatory states on page 1 of international applications disclosed in accordance with the PCT.

AT	Austria	CS	Czechoslovakia	KR	Republic of Korea	PL	Poland
AU	Australia	CZ	Czech Republic	KZ	Kazakhstan	PT	Portugal
BB	Barbados	DE	West Germany	LI	Liechtenstein	RO	Romania
BE	Belgium	DK	Denmark	LK	Sri Lanka	RU	Russian Federation
BF	Burkina Faso	ES	Spain	LU	Luxembourg	SD	Sudan
BG	Bulgaria	FI	Finland	LV	Latvia	SE	Sweden
BJ	Benin	FR	France	MC	Monaco	SI	Slovenia
BR	Brazil	GA	Gabon	MG	Madagascar	SK	Slovakian Republic
BY	Byelorussia	GB	Great Britain	ML	Mali	SN	Senegal
CA	Canada	GN	Guinea	MN	Mongolia	TD	Chad
CF	Central African Republic	GR	Greece	MR	Mauritania	TG	Togo
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CH	Switzerland	IE	Ireland	NE	Niger	US	USA
CI	Ivory Coast	IT	Italy	NL	Netherlands	UZ	Uzbekistan Republic
CM	Cameroon	JP	Japan	NO	Norway	VN	Vietnam
CN	PRC	KP	Democratic People's Republic of Korea	NZ	New Zealand		

Specification

CYCLOHEXANOL DERIVATIVE, AGENT AND COMPOSITION CONTAINING THE SAME FOR IMPARTING PLEASANTLY COOL FEELING, PROCESS AND INTERMEDIATE FOR PRODUCING THE DERIVATIVE

Technical Field

The present invention relates to a novel cyclohexanol derivative with a cooling effect and to a physiological cooling agent and physiological cooling composition containing said derivative. Further, the invention relates to a method for manufacturing said cyclohexanol derivative and to a novel benzylcyclohexyl ethyl derivative.

Known prior art chemical compounds with physiological cooling (coolant) action on the skin and nasal mucosae, ie, the so-called cooling effect, were oil of mint and L-menthol, the chief constituent thereof. They were added as aromas to food materials, beverages, toothpastes and tobacco and as cooling agents (coolants) to various cosmetic products and agents of topical application.

Thus, although L-menthol has a satisfactory cooling effect, it is prone to crystallization, and when used in some compositions, particularly when combined with poultices and tapes, it has the disadvantage that it crystallizes in the base, reducing the release of the medication and dictating the addition of additional solvent. Further, as is generally known, L-menthol has a strong odor which results in a loss of the elegant scent of cosmetic products with which it is combined.

L-Menthol is not entirely acceptable because it sublimates, and its characteristic mint odor spreads over a wide area even in small quantities, irritating the eyes and nasal mucosae and creating unfavorable environmental conditions in manufacturing industries that process L-menthol. Further, concerns have also recently been voiced by consumers using the products as well, because the mint odor tends to be offensive. Further, the sublimation tendency caused difficulties in maintaining the stability of products.

Recently, numerous patent applications have appeared concerning L-menthol derivatives and related compounds intended for odor attenuation. For example, Tokkai 1972-16647, Tokkai 1972-16649, Tokkai 1983-88334, Tokkai 1986-194049 and Tokkai 1990-290827 relate to menthol derivatives, while Tokkai 1983-93454, Tokkai 1983-95194 relate to tricyclic alcohols, and Tokkai 1985-136544 relates to tricyclic amides with cooling effects. However, while affording improvements in terms of odor, these substances were far inferior to L-menthol in the strength of their cooling effect. Hence, while physiological cooling agents other than L-menthol produced a good cooling effect in the oral mucosae, they had inadequate cooling action on the skin.

Thus, prior-art product formulations containing the aforementioned L-menthol and related products for use as cosmetics and medications are not completely adequate products because of drawbacks related to various aspects: 1) physiological cooling effect, 2) durability of cooling effect, 3) peculiar odor (mint odor), 4) instability in the product, 5) solubility.

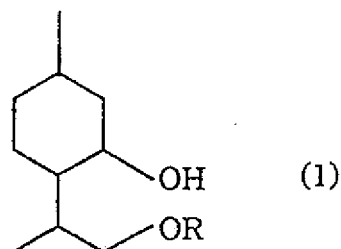
Thus, the goal of the invention is to devise a cooling compound and physiological cooling composition containing it, characterized by the fact that it has the following useful attributes: 1) affords an adequate cooling effect, 2) has no mint odor, 3) does not sublime at ordinary temperatures, 4) does not crystallize in the base, and 5) has good solubility in various bases, when used to develop various products such as cosmetics for oral and topical use and medications for oral use. ✓

Disclosure

The inventors conducted intensive research to achieve this goal and discovered that the novel cyclohexanol derivative with the above-listed structural formula has a physiological cooling action

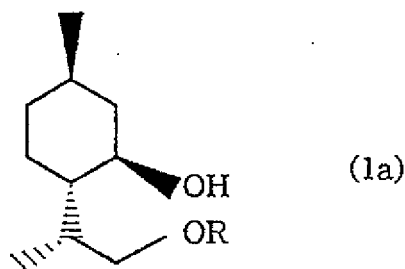
equivalent to that of L-menthol, with adequate action on both the oral mucosae and the skin, but has the superior property of almost completely lacking the odor of L-menthol and oil of mint. The invention is based on this discovery.

Thus, the cyclohexanol derivative has the following general formula (1)



where R is a linear or branched alkyl with a carbon number of 1-5.

The above inventive cyclohexanol derivative is the compound described at the end of this document, which was first discovered by the present inventors. Its formal name is 2-(2-alkoxy-1-methyl ethyl)-5-methylcyclohexanol. This compound includes several stereoisomers, all of which have strong cooling action and almost no odor. The cyclohexanol derivative (1R,2S,5R,8R)-2-(2-alkoxy-1-methyl ethyl)-5-methylcyclohexanol represented by the following formula (1a)



where R is a linear or branched alkyl with a carbon number of 1-5, is desirable with regard to the durability of the cooling action.

Examples of linear or branched alkyls with carbon numbers of 1-5 as represented by R in the above general formulas (1) and (1a) are methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, sec-butyl, tert-butyl, *n*-pentyl, isopentyl, sec-pentyl, tert-pentyl and neopentyl; methyl, ethyl, isopropyl, tert-butyl, although *n*-pentyl is preferred, and methyl is particularly preferred.

Inventive physiological cooling agents and physiological cooling compositions are described in the following.

The inventive physiological cooling agent contains the cyclohexanol derivative represented by the above general formula (1). Thus, because the inventive cyclohexanol derivative has a physiological cooling action itself, it can be used alone or in combination with other known cooling agents as a physiological cooling agent. Further, any of the various stereoisomers of the above-represented cyclohexanol derivative can be used singly or in combination with others, although the cyclohexanol derivative represented by the above general formula (1a) is preferred.

Thus, many applications may be contemplated for the inventive cyclohexanol derivative as a physiological cooling agent, for example, in pharmaceuticals, non-pharmaceuticals, foods and cosmetics, and various physiological cooling compositions containing this derivative can thus be

obtained thanks to the invention. Thus, the inventive physiological cooling composition is a product containing the cyclohexanol derivative represented in the above general formula (1).

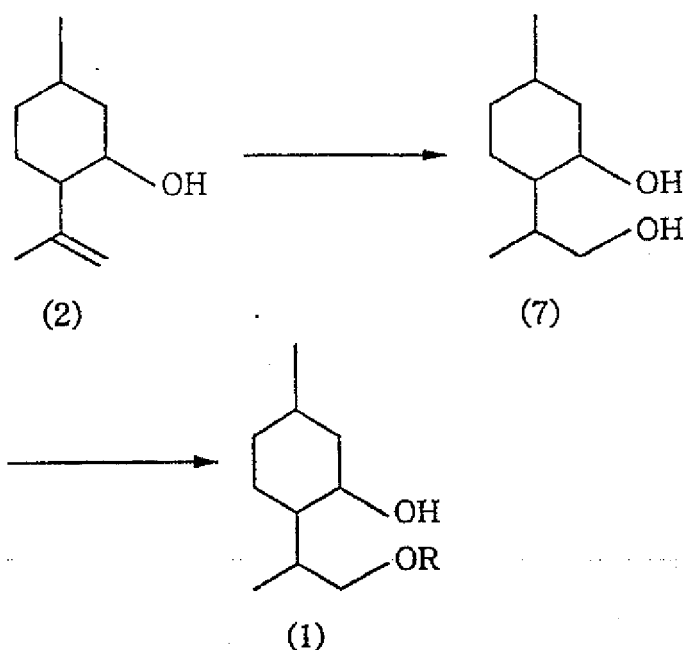
Hence, the inventive physiological cooling agent can be used specifically in a cooling composition to confer a cooling effect by adding it to: 1) pharmaceuticals such as ointments, creams, gels, lotions, ready-made dressings, tapes and internal medications; 2) cosmetics such as powders, hair tonic, shampoo and lipstick; 3) oral hygiene products such as toothpaste; and 4) food products such as chewing gum, candy, frozen desserts and soft drinks.

The ingredients used other than the inventive physiological cooling composition are not particularly limited. Known bases, active principles and the like can be combined with it by appropriate processes. Further, preservatives, antioxidants, scents, pigments or surfactants can be combined with the inventive physiological cooling composition as long as they do not impair the above-described cyclohexanol derivative's physiological cooling effect. When the inventive physiological cooling composition is used in various products such as pharmaceuticals and cosmetics, known medications can be appropriately added as pharmaceutically active constituents.

Although the content of the above-specified cyclohexanol derivative in the inventive physiological cooling composition is not particularly limited, it is preferably used in the range of 0.001-10 wt%.

Because the inventive cyclohexanol derivative is superior in all of the above-listed features 1-5, both the inventive physiological cooling agents and physiological cooling compositions containing this derivative have virtually no mint odor and a satisfactory cooling action on the skin together with a durable action with rapid onset of said action.

The method for manufacturing the inventive cyclohexanol derivative is explained in the following. The inventive cyclohexanol derivative can be synthesized, for example, from isopregol starting material according to the following reaction formula:



where R is a linear or branched alkyl with a carbon number of 1-5.

Thus, isopregol (2) and sodium borate were dissolved in a solvent such as diethyl ether, tetrahydrofuran or diglyme, and trifluoroboroethylate was added dropwise. After 1-2 hr, water was added to this mixture, followed by sodium hydroxide solution and aqueous hydrogen peroxide solution, and the mixture was thoroughly stirred. The reaction mixture obtained was extracted, for example, with ether, and the solvent was distilled off to obtain the diol (7).

Next, the targeted cyclohexanol derivative (1) is obtained by dissolving diol (7) in a solvent such as dimethylformamide, dimethyl sulfoxide, dimethoxyethane or tetrahydrofuran and subsequently adding a base such as sodium hydride, silver oxide, barium oxide, sodium hydroxide, triethylamine, calcium carbonate or sodium amine, after which the corresponding halogenated alkyl is added dropwise in an equimolar amount and the system is reacted over a time ranging from several hours to several tens of hours at a temperature ranging from -10 to 100°C.

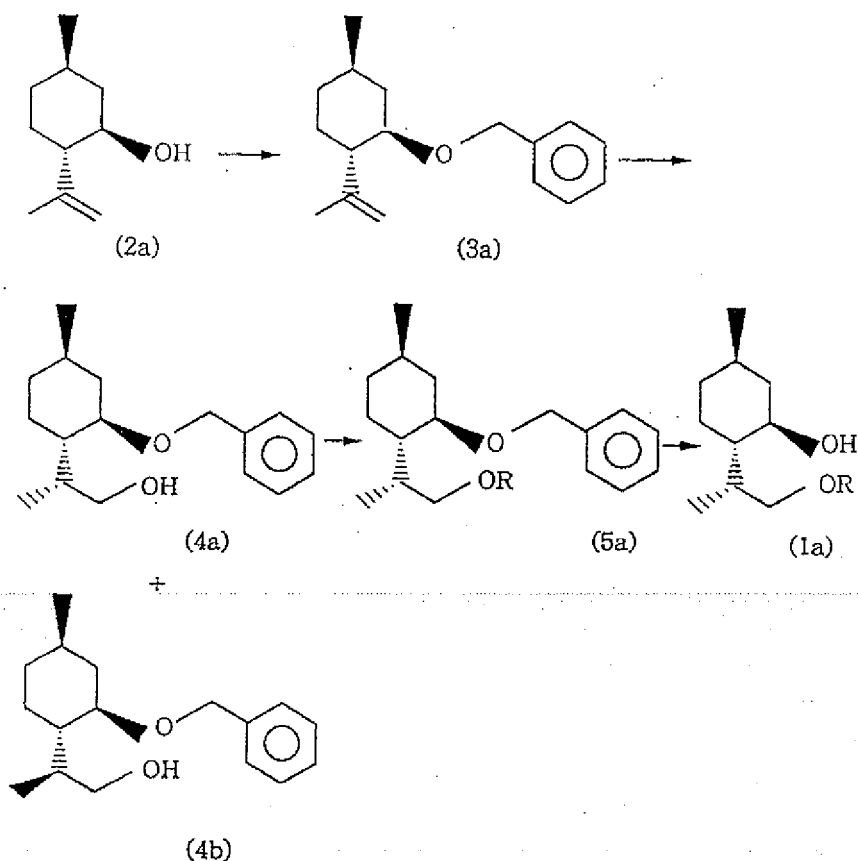
The inventive cyclohexanol derivative can be obtained either as a mixture of various stereoisomers or as a single stereoisomer by procedures such as column separation or by choice of starting materials to get an appropriate combination.

However, methods like column separation are time-consuming and not desired as industrial methods, and the inventors therefore created a novel, efficient manufacturing method for selectively obtaining (1R, 2S, 5R, 8R)-2-(2-alkoxy-1-methyl ethyl)-5-methylcyclohexanol represented by the above general formula (1a), which is a particularly desirable inventive cyclohexanol derivative.

To do so, the inventors conducted intensive research aimed at devising a method of synthesizing the cyclohexanol derivative represented by the above general formula (1a) in an industrially advantageous manner and discovered that the above-specified derivative could be manufactured highly efficiently and cheaply in high purity from starting material consisting of (-)-isopregol by using a specific reaction process.

The inventive method for manufacturing the cyclohexanol derivative of general formula (1a) is described in the following.

The reaction in the inventive method is represented by the following reaction scheme.



where R is a linear or branched alkyl with a carbon number of 1-5.

Thus, a salt is first formed by reacting (-)-isopregol (2a) and metallic sodium or sodium hydride in a benzenic solvent such as triene or xylene and reacting for 3-24 hr at ambient temperature. A halogenated benzyl compound such as benzyl chloride or benzyl bromide is then added dropwise while heating. After this addition, the system is left standing for 1-12 hr at room temperature to complete the reaction. After the reaction solution is cooled, water is mixed with it and the organic phase is separated, after which the solvent is drained and vacuumed off to obtain Compound (3a). During this reaction, the above-specified solvent is used in an amount 1-10 times that of the (-)-isopregol, by weight. Further, the amounts of metallic sodium or sodium hydride and of the halogenated benzyl are each preferably 1-2 times the molar quantities of (-)-isopregol.

Compound (3a) obtained in this way can be transformed to Compounds (4a,b) by a hydroboration-hydrogen peroxide oxidation reaction under conditions well-known to those skilled in the art. Thus, a B-H bond is added to the inner olefin of Compound (3a) by use of diborane (for example, in the form of a diborane-THF complex or diborane-methyl sulfate complex), diisopinocampheyl, 9-borabicyclo-(3.3.1)-nonane (9-BBN), dithiamyl borane, etc), and oxidation is done with hydrogen peroxide to obtain the novel target compound (4a,b) in a high yield.

Preferably, the diborane is formed inside or outside the system by reacting sodium borohydride and any of certain acids (for example, boron trifluoride etherate, aluminum chloride, sulfuric acid or dimethyl sulfate) and an organic solvent chosen from among THF, diethyl ether and dimethoxyethane. Thus, Compound (3a) is advantageously dissolved in a 0.5—20-fold, more preferably 1—10-fold amount, by weight, of organic solvent (preferably tetrahydrofuran), and, inside or outside the [reaction] system, a preferably 1—1.5-fold molar quantity of sodium hydroboride as against Compound (3a), and a preferably 1—1.5-fold molar quantity of the acid, as against the sodium hydroboride, is used to form the diborane. Stirring is continued with a temperature not to exceed 40°C inside the vessel, and thorough stirring is done for another 1-3 hr after the diborane is formed. Subsequently, an aqueous solution of 3 M of sodium hydroxide, preferably in a 1—2-fold quantity by weight as against Compound (3a), is added to the reaction system, and an equal amount of 30% hydrogen peroxide is gradually added dropwise with the temperature in the reaction vessel controlled so as not to exceed 40°C. After the dropwise addition was completed, the reaction liquid was stirred at room temperature for 0.5-3 hr and the organic phase was separated. The reaction product was then extracted from the aqueous phase with tetrahydrofuran, and added to the previously separated organic phase. After the organic phase was dried, the solvent was distilled off to obtain a mixture of crystalline Compound (4a) and liquid Compound (4b).

In the above-described reaction, the formation of Compound (4a) takes precedence over that of Compound (4b), and while Compound (4a) is crystallized, Compound (4b) remains in liquid form, so Compound (4a) can be readily obtained alone by rinsing with a solvent such as hexane in which it does not dissolve.

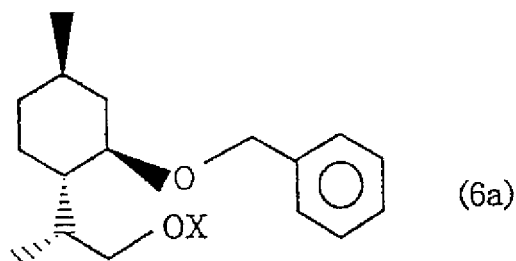
Compound (4a) is derivatized to Compound (5a) by an alkylating agent, for example, a methylating agent, in the presence of an organic solvent. As the organic solvent one can use, for example, N,N-dimethylformamide, dimethyl sulfate, tetrahydrofuran, dioxane or dimethoxyethane, preferably in a 1—20-fold, more preferably 2—10-fold, quantity, by weight, as against Compound (4a). Further, while sodium hydride, potassium *tert*-butoxide and the like can be used as the base, any base that promotes alkylation may be used. Alkylating agents that may be used include alkyl iodides, alkyl chlorides, aromatic alkyls and dialkyl sulfate, which are preferably used in 1—2-fold molar quantities as against Compound (4a). After the reaction is completed, the reaction product is neutralized by pouring it into water, then extracted with a suitable solvent, and the layer of organic phase is rinsed with water, dried, then concentrated to obtain novel Compound (5a) represented at the

end of this document. Further, Compound (5a) may also be refined as desired, for example, by vacuum distillation or column chromatography.

The reaction leading from Compound (5a) to Compound (1a) produces the inventive cyclohexanol derivative represented by General Formula (1a) using debenzylating agents of the palladium-carbon type as a catalyst for catalytic hydrogenation (debenzylation) of Compound (5a) using an acid such as sulfuric, hydrochloric, acetic or perchloric acid as a promoter in a solvent such as ethanol, methanol, acetic acid, dioxane or cyclohexane. The solvent is preferably used in a 1—20-fold, more preferably 2—5-fold quantity by weight as against Compound (5a). The concentration of the acid used is preferably in the range of 0.1-2 N, below which the reaction tends to proceed too slowly, and above which side reactions readily occur in addition to the targeted reaction. The debenzylating agent is preferably used in a 1—10-fold quantity by weight as against Compound (5a). The reaction may be conducted at ambient pressure, but preferably at a pressure of 2-5 kg/cm².

The inventors discovered that the compounds represented by the above formulas (4a) and (5a) are effective novel intermediates in the manufacture of the cyclohexanol derivatives represented by General Formula (1a) by the above-described inventive method. Thus, the inventive additionally relates to an intermediate for manufacturing cyclohexanol derivatives. An inventive novel benzyl cyclohexyl ether derivative is described as follows.

The inventive benzyl cyclohexyl ether derivative is represented by the following general formula (6a)



where X is H or a linear or branched alkyl with a carbon number of 1-5.

In the above general formula (6a), X is either hydrogen or an alkyl group identical with R in the above general formula (1). The compound in which X is hydrogen corresponds to the above-described compound (4a), while the compound in which X is an alkyl corresponds to the above-described compound (5a). As stated above, the inventive benzyl cyclohexyl ether derivative is extremely useful as an intermediate in the industrially efficient manufacture of the inventive cyclohexanol derivative represented by General Formula (1a).

Preferred Embodiments of the Invention

The invention is described in detail in the following on the basis of embodiments but is not limited thereto.

Reference Example 1. Synthesis of (1R,2S,5R)-2-(2-Hydroxy-1-Methyl Ethyl)-5-Methylcyclohexanol

In a 1 L 3-necked flask equipped with a cooling coil, a dropping funnel, a thermometer and a magnetic stirrer, 5.1 g (0.13 mol) of sodium borohydride, 700 mL of diglyme and 50.0 g (0.32 mol) of (-)-isopregol were introduced. In a water bath, 23.0 mL (0.18 mol) of boron trifluoride was added and the contents were stirred for 15 min (to form a precipitate). After stirring the contents for an

additional hour, the excess hydroxide was dissolved in 50 mL of water. In a 30-50°C water bath, 40 mL of 3 M aqueous sodium hydroxide solution was added to the organic borane produced by the above-described reaction, after which 40 mL of a 30% hydrogen peroxide solution was added, and the system was thoroughly stirred for 30 min. The reaction product was extracted from the above-described reaction solution with 1 L of ether and the diglyme was removed by washing 5 times with 1 L each of cold water. After this ether phase was dried with anhydrous magnesium sulfate, 45.0 g (80.8% yield) of (1R,2S,5R,8R)-2-(2-hydroxy-1-methyl ethyl)-5-methylcyclohexanol was obtained in the form of white crystals by distilling off the solvent (see *Helv. Chim. Acta.*, **50** (21), 153 (1967)).

Reference Example 2. Synthesis of (1R,2S,5R,8R)-2-(2-Hydroxy-1-Methyl Ethyl)-5-Methylcyclohexanol

30.0 g of the compound obtained in Reference Example 1 was column-separated using a 1:1 solution of chloroform:ethyl acetate, and the solvent was then distilled off to obtain 24.7 g (82.3% yield) (1R,2S,5R,8R)-2-(2-hydroxy-1-methyl ethyl)-5-methylcyclohexanol in the form of white crystals.

Embodiment 1. Synthesis of (1R,2S,5R)-2-(2-Methoxy-1-Methyl Ethyl)-5-Methylcyclohexanol

20.0 g (0.12 mol) of the (1R,2S,5R)-2-(2-hydroxy-1-methyl ethyl)-5-methylcyclohexanol obtained in Reference Example 1 was dissolved in 100 mL of dimethylformamide and 3.3 g (0.14 mol) of sodium hydride was then added. The resulting mixture was stirred for 30 min, 19.8 g (0.14 mol) of methyl iodide was then added dropwise, and stirring was continued for 24 hr at room temperature. After the reaction was completed, 300 mL of water was stirred into the reaction liquid, and the reaction product was extracted with ether. The ether phase was then dried with anhydrous magnesium sulfate, and 19.5 g (87.4% yield) of (1R,2S,5R)-2-(2-methoxy-1-methyl ethyl)-5-methylcyclohexanol was obtained as a colorless liquid by distilling off the solvent. The compound's MS analysis data and NMR data are as follows.

MS (M/e): 187 (M + 1)

NMR (CDCl₃, ppm):

0.84—1.01 (8H; 3-H_{ax}, 4-H_{ax}, 7-CH₃, 9-CH₃)

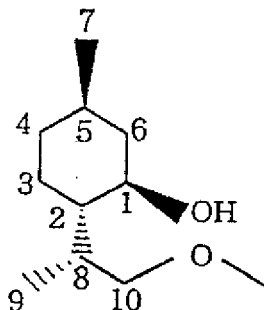
1.09—1.68 (5H; 2-H, 3-Heq, 4-Heq, 5-H, 6-H_{ax})

1.92—2.06 (2H; 6-Heq, 8-H)

3.26—3.71 (6H; 1-H, -OCH₂-, -OCH₃)

Embodiment 2. Synthesis of (1R,2S,5R,8R)-2-(2-Methoxy-1-Methyl Ethyl)-5-Methylcyclohexanol

18.0 g of the compound obtained in Embodiment 1 was subjected to column separation using 1:1:2 ethyl acetate:chloroform:hexane, and 14.3 g (79.7% yield) of (1R,2S,5R,8R)-2-(2-methoxy-1-methyl ethyl)-5-methylcyclohexanol was obtained in the form of a colorless liquid by distilling off the solvent. The stereochemical formula, MS analysis data and NMR data are given below.



MS (M/e): 187 (M + 1)

NMR (CDC13, ppm)::

0.80—1.01 (8H; 7-CH₃, 9-CH₃, 3-Hax, 4-Hax)

1.07—1.69 (5H; 2-H, 3-Heq, 4-Heq, 5-H, 6-Hax)

1.92—2.04 (2H; 8-H, 6-Heq)

3.27—3.45 (6H; -OCH₂-, -OCH₃, 1-H)

3.72 (1H; -OH)

Embodiment 3. Synthesis of (1R,2S,5R,8R)-2-(2-Methoxy-1-Methyl Ethyl)-5-Methylcyclohexanol

Except for the fact that 20.0 g (0.12 mol) of the (1R,2S,5R,8R)-2-(2-hydroxy-1-methyl ethyl)-5-methylcyclohexanol obtained in Reference Example 2 was used as the starting material, the same procedure was used as in Example 1, and 19.6 g (90.5% yield) of (1R,2S,5R,8R)-2-(2-methoxy-1-methyl ethyl)-5-methylcyclohexanol was obtained as a colorless liquid. The compound obtained was identical with that of Embodiment 2.

Embodiment 4. Synthesis of (1R,2S,5R)-2-(2-Ethoxy-1-Methyl Ethyl)-5-Methylcyclohexanol

20.0 g (0.12 mol) of (1R,2S,5R)-2-(2-hydroxy-1-methyl ethyl)-5-methylcyclohexanol was dissolved in 100 mL of dimethylformamide, and 3.3 g (0.14 mol) of sodium hydride was then added. After mixing this mixture for 30 min, 21.8 g (0.14 mol) of ethyl iodide was added dropwise, and stirring was continued at room temperature for 24 hr. After the reaction was completed, 300 mL of water was added to the reaction liquid and stirring was continued, after which the reaction product was extracted with ether. The ether phase was then dried with anhydrous magnesium sulfate, and 20.1 g (86.4% yield) of (1R,2S,5R)-2-(2-ethoxy-1-methyl ethyl)-5-methylcyclohexanol was obtained as a colorless liquid by distilling off the solvent. The MS analysis and NMR data of the compound obtained are as follows.

MS (M/e): 201 (M + 1)

NMR (CDC13, ppm):

0.81—1.03 (8H; 3-Hax, 4-Hax, 7-CH₃, 9-CH₃)

1.11—1.69 (8H; 2-H, 3-Heq, 4-Heq, 5-H, 6-Hax, -OCH₂CH₃)

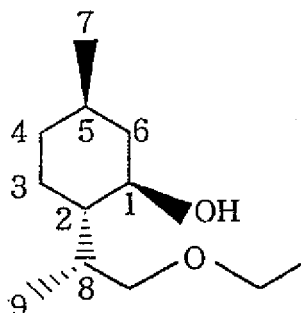
1.90—2.03 (2H; 6-Heq, 8-H)

3.23—3.68 (5H; 1-H, -OCH₂CH-, -OCH₂CH₃)

Embodiment 5. Synthesis of (1R,2S,5R,8R)-2-(2-Ethoxy-1-Methyl Ethyl)-5-Methylcyclohexanol

18.0 g of the compound obtained in Embodiment 3 was column-separated using a 1:1:2 ethyl acetate:chloroform:hexane mixture, and the solvent was distilled off to obtain 14.9 g (82.7% yield)

of (1R,2S,5R,8R)-2-(2-ethoxy-1-methyl ethyl)-5-methylcyclohexanol as a colorless liquid. The stereochemical formula and the MS and NMR data of the compound obtained are as follows.



MS (M/e): 201 (M + 1)

NMR (CDS13, ppm):

0.80—1.01 (8H; 7-CH₃, 9-CH₃, 3-H_{ax}, 4-H_{ax})

1.10—1.68 (8H; 2-H, 3-Heq, 4-Heq, 5-H, 6-H_{ax}, -OCH₂CH₃)

1.89—2.03 (2H; 6-Heq, 8-H)

3.32—3.55 (5H; 1-H, -OCH₂-, -OCH₂CH₃)

4.14 (1H; -OH)

Embodiment 6. Synthesis of (1R,2S,5R)-2-(2-Isopropoxy-1-Methyl Ethyl)-5-Methylcyclohexanol

20.0 g (0.12 mol) of (1R,2S,5R)-2-(2-hydroxy-1-methyl ethyl)-5-methylcyclohexanol was dissolved in 100 mL of dimethoxyethane, and 3.3 g (0.14 mol) of sodium hydride was added. The mixture was stirred for 30 min, after which 23.7 g (0.14 mol) of isopropyl iodide was added, and stirring was continued at room temperature for 24 hr. After the reaction was completed, 300 mL of water was stirred into the reaction liquid, and the reaction product was then extracted with ether. The ether phase was then dried with anhydrous magnesium sulfate to obtain 18.3 g (73.6% yield) of (1R,2S,5R)-2-(2-methoxy-1-methyl ethyl)-5-methylcyclohexanol in the form of a colorless liquid. The MS analysis and NMR data of the compound obtained are as follows.

MS (M/e): 215 (M + 1)

NMR (CDC13, ppm):

0.85—1.05 (8H; 3-H_{ax}, 4-H_{ax}, 7-CH₃, 9-CH₃)

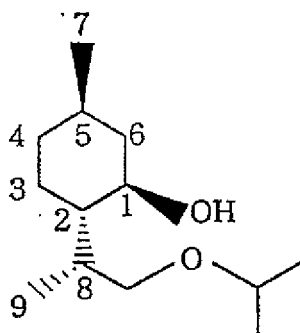
1.13—1.70 (11H; 2-H, 3-Heq, 4-Heq, 5-H, 6-H_{ax}, -OCH(CH₃)₂)

1.95—2.11 (2H; 6-Heq, 8-H)

3.19—3.75 (4H; 1-H, -OCH₂-, -OCH(CH₃)₂)

Embodiment 7. Synthesis of (1R,2S,5R,8R)-2-(2-Isopropoxy-1-Methyl Ethyl)-5-Methylcyclohexanol

15.0 g of the compound obtained in Embodiment 5 was column-separated using a 1:1:2 ethyl acetate:chloroform:hexane mixture, and the solvent was then distilled off to obtain 12.5 g (83.1% yield) of (1R,2S,5R,8R)-2-(2-isopropoxy-1-methyl ethyl)-5-methylcyclohexanol. The stereochemical formula, MS analysis and NMR data of the compound obtained are as follows.



MS (M/e): 215 (M + 1)

NMR (CDC13, ppm):

0.80—1.03 (8H; 7-CH₃, 9-CH₃, 3-Hax, 4-Hax)

1.11—1.68 (11H; -OCH(CH₃)₂, 2-H, 3-Heq, 4-Heq, 5-H, 6-Hax)

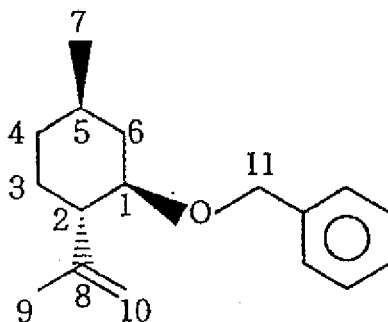
1.85—2.02 (2H; 6-Heq, 8-H)

3.33—3.65 (4H; 1-H, -OCH₂-, -OCH(CH₃)₂)

4.39 (1H; -OH)

Reference Example 3. Synthesis of Benzyl (1R,2S,5R)-2-Isopropenyl-5-Methylcyclohexanol Ether (Compound (3a))

230 mL of triene, 77.0 g (0.5 mol) of (-)-isopregol and 12.7 g (0.55 mol) of metallic sodium were stirred with heating and held at reflux temperature for 18 hr to form a salt. Subsequently, 82.3 g (0.65 mol) of benzyl chloride was added dropwise over 1 hr and the reaction was conducted for 2 hr at reflux temperature. After the vessel and its contents were cooled, 300 mL of water was added and the organic phase was separated. The organic phase was washed with an aqueous saline solution and dried with anhydrous magnesium sulfate, after which the triene was recovered and vacuum distillation was performed to obtain 108.6 g (89% yield) of compound (3a). The stereochemical formula, boiling point, MS analysis data and NMR data are as follows.



b. p. = 118—121°C/3 mmHg

MS (M/e): 244 (M +)

NMR (CDC13, ppm):

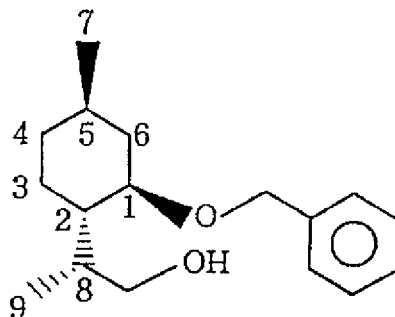
0.82—1.05 (5H; 3-Hax, 4-Hax, 7-CH₃)

1.21—1.71 (7H; 9-CH₃, 3-Heq, 4-Heq, 5-H, 6-Hax)

2.02—2.21 (2H; 2-H, 6-Heq)
 3.22—3.35 (1H; 1-H)
 4.39—4.82 (4H; -OCH₂C₆H₅, C=CH₂)
 7.18—7.35 (5H; benzene ring)

Embodiment 8. Synthesis of Benzyl (1R,2S,5R,8R)-2-(2-Hydroxy-1-Methyl Ethyl)-5-Methylcyclohexanol Ether (Compound (4a))

61 g (0.25 mol) of Compound (3a) obtained in Reference Example 3 and 9.5 g (0.25 mol) of sodium borohydride were dissolved in 100 mL of anhydrous THF, after which 31.5 g (0.25 mol) of dimethyl sulfate was added dropwise with the temperature controlled so as not to exceed 40°C, and mixing was done for 2 hr at room temperature. The reaction liquid was then cooled, and 100 mL of water was carefully added dropwise. After this dropwise addition, 100 mL of 3 M NaOH aqueous solution was added to the reaction liquid, and 100 mL of 30% hydrogen peroxide was then added with the internal temperature controlled so as not to exceed 40°C, and the system was then stirred for 30 min. Subsequently, the organic phase was separated, and the reaction product was extracted from the aqueous phase using 500 mL of *n*-hexane, after which the organic phase was added. The organic phase was washed with water and saturated aqueous table salt solution, dried with anhydrous magnesium sulfate, and the solvent was distilled off. The crystals obtained in this way were washed with *n*-hexane to obtain 47.8 g (73% yield) of Compound (4a). The stereochemical formula, melting point and MS analysis and NMR data of the compound obtained are as follows.



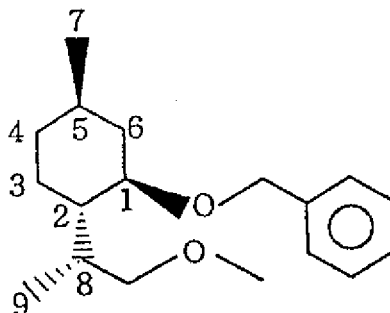
m. p. = 82.5—83.5°C
 MS (M/e): 262 (M +)
 NMR (CDC13, ppm):
 0.82—0.99 (8H; 3-Hax, 4-Hax, 7-CH₃, 9-CH₃)
 1.12—1.94 (6H; 2-H, 3-Heq, 4-Heq, 5-H, 6-Hax, 8-H)
 2.24 (1H; 6-Heq)
 2.59 (1H; -OH)
 3.22—3.54 (3H; 1-H, -OCH₂OH)
 4.36—4.70 (2H; -OCH₂C₆H₅)
 7.24—7.36 (5H; benzyl ring)

Embodiment 9. Synthesis of Benzyl (1R,2S,5R,8R)-2-(2-Methoxy-1-Methyl Ethyl)-5-Methylcyclohexanol Ether (Compound (5a))

An 80 mL DMF solution of 40 g (153 mmol) of Compound (4a) obtained in Embodiment 8 was added dropwise with ice cooling to 40 mL of a DMF solution of 9.2 g (230 mmol, 60% in oil)

sodium hydride. After this dropwise addition, the reaction liquid was stirred for 1 hr, and 32.6 g (230 mmol) of methyl iodide was added dropwise over 30 min with ice cooling. After the reaction liquid had been stirred for 3 hr at room temperature, it was carefully poured into ice water, and the reaction product was extracted with hexane. After the organic phase was separated, it was washed with an aqueous table salt solution and dried with anhydrous magnesium sulfate, and the solvent was then recovered. The residue thus obtained was distilled off under vacuum to obtain 42.1 g (90% yield) of Compound (5a).

The stereochemical formula, boiling point and MS analysis and NMR data are as follows.



b. p. = 188—191°C/3 mmHg

MS (M/e): 276 (M +)

NMR (CDC13, ppm):

0.79—1.72 (13H; 2-H, 3-Hax, 3-Heq, 4-Hax, 4-Heq, 5-H, 6-Hax, 7-CH3, 9-CH3)

2.13—2.32 (2H; 6-Heq, 8-H)

3.13—3.36 (6H; 1-H, -CH₂OCH₃, -OCH₃)

4.38—4.68 (2H; -OCH₂C₆H₅)

7.21—7.37 (5H; benzene ring)

Embodiment 10. Synthesis of (1R,2S,5R,8R)-2-(2-Methoxy-1-Methyl Ethyl)-5-Methylcyclohexanol (Compound (1a))

45.0 g (163 mmol) of Compound (5a) obtained in Embodiment 9 was dissolved in 120 mL of 1 N hydrochloric acid-ethanol mixture in a pressure bottle, and 2.25 g (5% by weight) 5% palladium-carbon was carefully added. The reaction vessel was pressurized with hydrogen gas to 3 kg/cm² and stirred at room temperature. After 3 hours, with determination of the hydrogen absorption, the content of the reaction vessel was restored to ambient pressure and the reaction was stopped. The catalyst was filtered off, the solvent was concentrated, and the reaction product was extracted with 500 mL of ether, then washed with 500 mL of 1 N sodium hydroxide solution. The ether was drained, then distilled off under vacuum to obtain 27.9 g (92.0% yield) of (1R,2S,5R,8R)-2-(2-methoxy-1-methyl ethyl)-5-methylcyclohexanol (Compound (1a)).

Formulation 1. Lotion

	(wt%)
ethanol	59.0
purified water	35.0
propylene glycol	5.0
(1R,2S,5R)-2-(2-methoxy-1-methyl ethyl)-5-methylcyclohexanol	1.0

A cooling agent was prepared with the above formulation. Applied to the skin, it conferred a bracing menthol-like coolness.

Formulation 2. Hair Tonic

	(wt%)
ethanol	52.0
jojoba oil	0.4
polyoxyethylene sorbitan laurate	1.2
propylene glycol	1.2
trichlosan	0.1
pigment	trace
(1R,2S,5R)-2-(2-methoxy-1-methyl ethyl)-5-methylcyclohexanol	0.5
purified water	balance

A hair tonic was prepared by uniformly mixing the above formulation. When this hair tonic was applied to the scalp, a refreshing cooling sensation remained after the cooling effect produced by evaporation of the ethanol.

Formulation 3. Skin Lotion

	(wt%)
ethanol	20.0
propylene glycol	5.0
glycerin	4.5
methyl paraoxybenzoate	0.1
fragrance	0.2
purified water	70.0
(1R,2S,5R)-2-(2-ethoxy-1-methyl ethyl)-5-methylcyclohexanol	0.2

A skin lotion was prepared by mixing the above-listed ingredients. When applied to the skin, it conferred a bracing cooling effect to the skin without irritation.

Formulation 4. Toothpaste

	(wt%)
calcium hydrogen phosphate	50.0
carboxymethyl cellulose	1.0
sodium lauryl sulfate	2.0
glycerin	25.0
saccharin	0.2
fragrance	0.8
(1R,2S,5R)-2-(2-methoxy-1-methyl ethyl)-5-methylcyclohexanol	0.1
purified water	balance

A toothpaste was prepared by mixing the above-listed ingredients. When used, it conferred a refreshing cooling effect throughout the mouth.

Formulation 5. Shampoo

	(wt%)
sodium lauryl sulfate	12.0
purified water	87.5
(1R,2S,5R)-2-(2-methoxy-1-methyl ethyl)-5-methylcyclohexanol	0.5

A shampoo was prepared by mixing and dispersing the above-listed ingredients. When this shampoo was used, it left a bracing cooling effect on the skin.

Formulation 6. Cream

	(wt%)
liquid paraffin	10.0
medium chain fatty acid triglycerides	5.0
polyethylene glycol monostearate	3.0
glycerin	5.0
carboxyvinyl polymer	1.0
diisopropylamine	0.4
methyl paraoxybenzoate	0.2
(1R,2S,5R)-2-(2-methoxy-1-methyl ethyl)-5-methylcyclohexanol	2.0
purified water	balance

A cream was prepared by mixing the above-listed components. A refreshing effect was left at the place where it was applied to the skin.

Formulation 7. Ointment

	(wt%)
white vaseline	76.0
glycerin monostearate	10.0
tallow	10.0
silicone oil	1.0
(1R,2S,5R)-2-(2-methoxy-1-methyl ethyl)-5-methylcyclohexanol	3.0

An ointment was prepared by mixing the above-listed ingredients. When applied to the skin, it conferred a menthol-like cooling effect.

Formulation 8. Poultice

	(wt%)
gelatin	5.0
sorbitol	10.0
carboxymethyl cellulose	3.5
glycerin	25.0
kaolin	7.0
sodium polyacrylate	3.0
(1R,2S,5R)-2-(2-methoxy-1-methyl ethyl)-5-methylcyclohexanol	0.5
purified water	46.0

A poultice was prepared by mixing the above-listed components while heating to form a paste, which was then spread onto a cloth. The product had the same cooling on the skin effect as menthol.

Formulation 9. Poultice

	(wt%)
gelatin	6.0
polyvinyl alcohol	3.5
methoxyethylene-anhydrous maleic acid copolymer	2.5
glycerin	30.0
kaolin	5.0
sodium polyacrylate	2.0
(1R,2S,5R)-2-(2-isopropoxy-1-methyl ethyl)-5-methylcyclohexanol	0.5
purified water	50.0

A poultice was prepared by mixing the above-listed components while heating to form a paste, which was then spread onto a cloth. The product had the same cooling on the skin effect as menthol.

Formulation 10. Lotion

	(wt%)
ethanol	59.0
purified water	35.0
propylene glycol	5.0
(1R,2S,5R,8R)-2-(2-methoxy-1-methyl ethyl)-5-methylcyclohexanol	1.0

A cooling agent was prepared with the above formulation. Applied to the skin, it conferred a bracing menthol-like coolness.

Formulation 11. Hair Tonic

	(wt%)
ethanol	52.0
jojoba oil	0.4
polyoxyethylene sorbitan laurate	1.2
propylene glycol	1.2
trichlosan	0.1
pigment	trace
(1R,2S,5R,8R)-2-(2-methoxy-1-methyl ethyl)-5-methylcyclohexanol	0.5
purified water	balance

A hair tonic was prepared by uniformly mixing the above formulation. When this hair tonic was applied to the scalp, a refreshing cooling sensation remained after the cooling effect produced by evaporation of the ethanol.

Formulation 12. Skin Lotion

	(wt%)
ethanol	20.0
propylene glycol	5.0
glycerin	4.5
methyl paraoxybenzoate	0.1
fragrance	0.2
purified water	70.0
(1R,2S,5R,8R)-2-(2-ethoxy-1-methyl ethyl)-5-methylcyclohexanol	0.2

A skin lotion was prepared by mixing the above-listed ingredients. When applied to the skin, it conferred a bracing cooling effect to the skin without irritation.

Formulation 13. Toothpaste

	(wt%)
calcium hydrogen phosphate	50.0
carboxymethyl cellulose	1.0
sodium lauryl sulfate	2.0
glycerin	25.0
saccharin	0.2
fragrance	0.8
(1R,2S,5R,8R)-2-(2-methoxy-1-methyl ethyl)-5-methylcyclohexanol	0.1
purified water	balance

A toothpaste was prepared by mixing the above-listed ingredients. When used, it conferred a refreshing cooling effect throughout the mouth.

Formulation 14. Shampoo

	(wt%)
sodium lauryl sulfate	12.0
purified water	87.5
(1R,2S,5R,8R)-2-(2-methoxy-1-methyl ethyl)-5-methylcyclohexanol	0.5

A shampoo was prepared by mixing and dispersing the above-listed ingredients. When this shampoo was used, it left a bracing cooling effect on the skin.

Formulation 15. Cream

	(wt%)
liquid paraffin	10.0
medium chain fatty acid triglycerides	5.0
polyethylene glycol monostearate	3.0
glycerin	5.0
carboxyvinyl polymer	1.0
diisopropylamine	0.4
methyl paraoxybenzoate	0.2
(1R,2S,5R,8R)-2-(2-methoxy-1-methyl ethyl)-5-methylcyclohexanol	2.0
purified water	balance

A cream was prepared by mixing the above-listed components. A refreshing effect was left at the place where it was applied to the skin.

Formulation 16. Ointment

	(wt%)
white vaseline	76.0
glycerin monostearate	10.0
tallow	10.0
silicone oil	1.0
(1R,2S,5R,8R)-2-(2-methoxy-1-methyl ethyl)-5-methylcyclohexanol	3.0

An ointment was prepared by mixing the above-listed ingredients. When applied to the skin, it conferred a menthol-like cooling effect.

Formulation 17. Poultice

	(wt%)
gelatin	5.0
sorbitol	10.0
carboxymethyl cellulose	3.5
glycerin	25.0
kaolin	7.0
sodium polyacrylate	3.0
(1R,2S,5R,8R)-2-(2-methoxy-1-methyl ethyl)-5-methylcyclohexanol	0.5
purified water	46.0

A poultice was prepared by mixing the above-listed components while heating to form a paste, which was then spread onto a cloth. The product had the same cooling on the skin effect as menthol.

Formulation 18. Poultice

	(wt%)
gelatin	6.0
polyvinyl alcohol	3.5
methoxyethylene-anhydrous maleic acid copolymer	2.5
glycerin	30.0
kaolin	5.0
sodium polyacrylate	2.0
(1R,2S,5R,8R)-2-(2-isopropoxy-1-methyl ethyl)-5-methylcyclohexanol	0.5
purified water	50.0

A poultice was prepared by mixing the above-listed components while heating to form a paste, which was then spread onto a cloth. The product had the same cooling on the skin effect as menthol.

Formulation 19. Poultice

	(wt%)
gelatin	6.0
polyvinyl alcohol	3.5
methoxyethylene-anhydrous maleic acid copolymer	2.5
glycerin	30.0
kaolin	5.0
sodium polyacrylate	2.0
(1R,2S,5R,8R)-2-(2-ethoxy-1-methyl ethyl)-5-methylcyclohexanol	0.5
purified water	50.0

A poultice was prepared by mixing the above-listed components while heating to form a paste, which was then spread onto a cloth. The product had the same cooling on the skin effect as menthol.

Reference Example 1. Poultice

	(wt%)
gelatin	5.0
sorbitol	10.0
carboxymethyl cellulose	3.5
glycerin	25.0
kaolin	7.0
sodium polyacrylate	3.0
L-menthol	0.5
crotamiton	1.0
purified water	45.0

A poultice was prepared by mixing the above-listed ingredients while heating to form a paste, which was spread on a cloth. Crotamiton was used as a solubilizer for the L-menthol in this example.

Reference Example 2. Poultice

	(wt%)
gelatin	5.0
sorbitol	10.0
carboxymethyl cellulose	3.5
glycerin	25.0
kaolin	7.0
sodium polyacrylic acid	3.0
L-menthol	0.5
purified water	46.0

A poultice was prepared by mixing the above-listed ingredients while heating to form a paste, which was applied to a base cloth. Except for the fact that crotamiton, a solubilizer for L-menthol was not used, the composition of this reference example is the same as that of Reference Example 1.

Reference Example 3. Cream

	(wt%)
liquid paraffin	10.0
medium chain fatty acid triglycerides	5.0
polyethylene glycol monostearate	3.0
glycerin	5.0
carboxyvinyl polymer	1.0
diisopropylamine	0.4
methyl paraoxybenzoate	0.2
L-menthol	
purified water	2.0
	balance

A cream was prepared by mixing the above-listed components. Except for the fact that L-menthol was used instead of (1R,2S,5R,8R)-2-(2-methoxy-1-methyl ethyl)-5-methylcyclohexanol, this reference cream was the same as that of Formulation Example 15.

Test Example 1

The physiological cooling effect of 2-(2-methoxy-1-methyl ethyl)-5-methylcyclohexanol in a 0.01% petroleum ether solution was tested by applying it to the tips of the tongues and to the forearms of 10 healthy adult males. As a standard, a 0.01% petroleum ether solution of L-menthol was used. The results are shown in Table 1. The physiological cooling effect was rated on the following scale:

- +++ extremely strong cooling effect perceived
- ++ strong cooling effect perceived
- + cooling effect perceived
- cooling effect not perceived

Table 1

Cooling Agent Sample	Cooling Effects on the Tongue	Cooling Effects on the Inside Skin of the Forearm
2-(2-methoxy-1-methyl ethyl)-5-methylcyclohexanol (Embodiment 2)	+++	++
L-menthol	+++	++

As is evident from the results shown in Table 1, the inventive 2-(2-methoxy-1-methyl ethyl)-5-methylcyclohexanol had the same adequate cooling action as L-menthol on both the tip of the tongue and the skin.

Test Example 2

The physiological cooling effects and scents of the poultices of Formulation 8, 17, 18, 19 and Reference Example 1 were tested by applying these to the dorsal region of the forearms of 26 healthy male subjects. The ratings were made by testing the items listed in the following. The results are shown in Table 2. The procedure used for evaluation was to have the subjects use the following scale to report the pertinent test results for the various test items.

Test Items and Scale of Test Results

a) intensity of cooling

strong cooling	_____	3
little cooling	_____	2
no cooling	_____	1

b) durability of cooling

over 3 hours	_____	3
less than 3 hours	_____	2
less than 1 hour	_____	1

- c) speed of cooling
- | | | |
|-----------------|-------|---|
| within 5 min | _____ | 3 |
| within 5-10 min | _____ | 2 |
| over 10 min | _____ | 1 |
- d) intensity of odor
- | | | |
|-------------|-------|---|
| strong odor | _____ | 3 |
| weak odor | _____ | 2 |
| no odor | _____ | 1 |

The number of points assigned by the subjects' ratings for the 4 items listed above were totaled to obtain the averages for the 26 subjects in each item as shown in Table 2.

Table 2

Sample	Items Tested			
	Intensity of Cool Sensation	Duration of Cool Sensation	Speed of Onset of Cool Sensation	Intensity of Odor
Formulation 8 Poultice	2.9	2.9	2.8	1.1
Formulation 17 Poultice	2.9	3.0	2.9	1.1
Formulation 18 Poultice	2.8	3.0	2.7	1.1
Formulation 19 Poultice	2.8	3.0	2.8	1.1
Reference Example 1 Poultice	2.9	2.5	2.5	2.9

As we see from the results in Table 2, the poultice containing the inventive 2-(2-alkoxy-1-methyl ethyl)-5-methylcyclohexanol had a cooling effect equivalent to that of the L-menthol-containing poultice but had practically no odor.

Test Example 3

The poultices obtained in Formulation 8, 18, 19 and Reference Example 2 were stored at 5°C and investigated for crystallization with elapsing time. The results are shown in Table 3.

Table 3

Sample	Time Elapsed				
	start	1 day	3 days	7 days	14 days
Formulation 8 Poultice	○	○	○	○	○
Formulation 18 Poultice	○	○	○	○	○
Formulation 19 Poultice	○	○	○	○	○
Reference Example 2 Poultice	○	○	×	×	×

○: no crystallization observed

×: crystallization observed

As shown by the results in Table 3, while the L-menthol eventually crystallized in the poultice of Reference Example 2 which contained L-menthol as a cooling agent but had no solubilizer added, the inventive 2-(2-alkoxy-1-methyl ethyl)-5-methylcyclohexanol alone remains stable in dissolved form in the base, and consequently, the poultice containing the inventive cooling agent remained stable for an extended time period even without the addition of solubilizer.

Experimental Example 4

The creams of Formulation Example 15 and Reference Example 3 were applied to the facial skin of 20 subjects and tested comparatively for physiological cooling effects and odor. The items listed below were tested and rated. The results are shown in Table 4. The evaluation procedure was based on a 5-point rating of each test item according to the following 5-point scale.

Test Items, Distribution of Test Results and Scores

a) potency of cooling action

cooling to the point of painfulness 5
strong cooling action 4
appropriate cooling action 3
weak cooling action 2
no cooling action 1

b) duration of cooling effect

over 1 hr 5
over 30 min 4
over 10 min 3
over 5 min 2
only initial effect 1

- c) strength of odor
- | | |
|---------------------------------|---------|
| so strong it irritates the eyes | 5 |
| strong odor | 4 |
| has odor | 3 |
| faint odor | 2 |
| no odor | 1 |

Table 4 shows the averages of the various test items for 20 subjects based on the total scores for 4 items [sic].

Table 4

Sample	Test Item		
	Strength of Cooling Action	Duration of Cooling Action	Strength of Odor
cream of Formulation 15	4.0	4.8	1.6
cream of Reference Example 3	4.2	3.5	4.7

As shown by the results in Table 4, the cream containing the inventive (1R,2S,5R,8R)-2-(2-methoxy-1-methyl ethyl)-5-methylcyclohexanol had almost the same cooling action as the L-menthol-containing cream but was superior in terms of duration and odor.

Industrial Utility

The inventive 2-(2-alkoxy-1-methyl ethyl)-5-methylcyclohexanol has excellent properties, producing an adequate physiological cooling effect on both the oral mucosae and the skin but with virtually no odor in comparison to L-menthol, and remaining stably dissolved in various bases without the addition of solubilizer.

Thus, the use of the inventive cyclohexanol derivative produces, with virtually no odor, an adequate cooling action on the skin, etc, and affords a cooling agent with excellent duration and rapid onset of action.

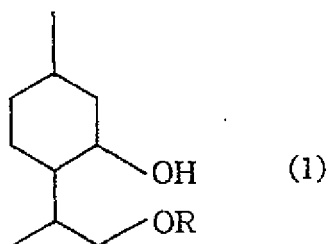
Further, the addition of the inventive cyclohexanol derivative to pharmaceutical products such as ointments, creams, gels, lotions, ready-made poultices, tapes and internal medicines; cosmetics such as powders, hair tonics, shampoos and lipsticks; oral hygiene agents such as toothpastes; and foods and beverages such as chewing gum, candy, frozen desserts and soft drinks affords an inventive cooling composition without odor and with a refreshing cooling action.

Further, the particularly preferred cyclohexanol derivative (1R,2S,5R,8R)-2-(2-methoxy-1-methyl ethyl)-5-methylcyclohexanol can be manufactured alone with high efficiency by a simple process using (-)-isopregol as the starting material by the inventive method. Thus, the inventive method is an industrially extremely advantageous method for manufacturing the inventive cyclohexanol derivative.

Further, in addition to the efficient manufacture of the inventive cyclohexanol derivative by the above-described inventive method, the inventive benzyl cyclohexanol derivative is an extremely useful intermediate.

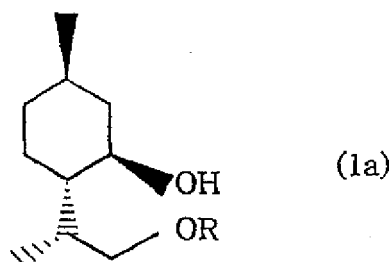
Claims

1. Cyclohexanol derivative with the following general formula (1)



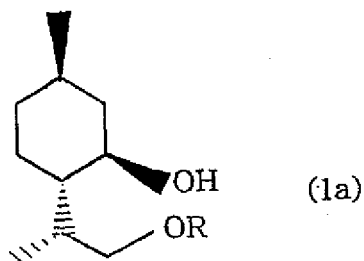
where R is a linear or branched alkyl with a carbon number of 1-5.

2. Physiological cooling agent containing the cyclohexanol derivative described in Claim 1.
3. Physiological cooling composition containing the cyclohexanol derivative described in Claim 1.
4. Cyclohexanol derivative with the following general formula (1a)

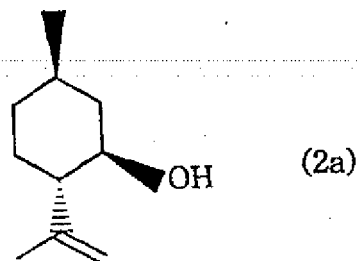


where R is a linear or branched alkyl with a carbon number of 1-5.

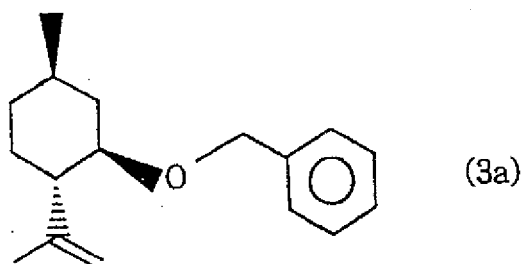
5. Method for manufacturing a cyclohexanol derivative of general formula (1a)



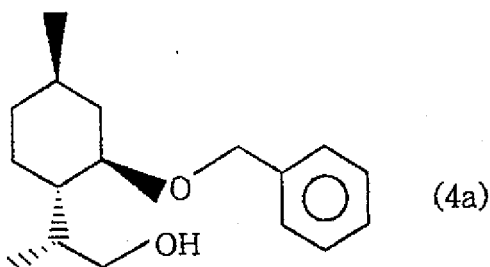
where R is a linear or branched alkyl with a carbon number of 1-5, characterized by the fact that (-)-isopregol of the following formula (2a)



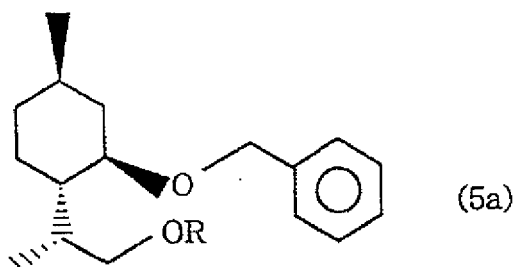
is reacted with a benzyl halide in the presence of metallic sodium or sodium hydride to produce a compound of the following formula (3a)



after which said compound (3a) is subjected to hydroboration to produce a compound of the following formula (4a)

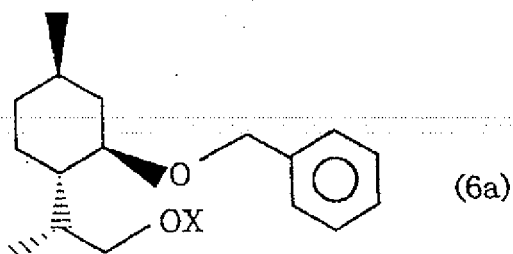


after which said compound (4a) is alkylated by an alkylating agent in the presence of a base to form a compound of the following general formula (5a)



where R is a linear or branched alkyl with a carbon number of 1-5, and said compound (5a) is catalytically hydrogenated in the presence of a debenzylating agent.

6. Benzyl cyclohexyl ether derivative of the following general formula (6a)



where X is H or a linear or branched alkyl with a carbon number of 1-5.

INTERNATIONAL SEARCH REPORT

International Application No.:

A. CLASSIFICATION OF SUBJECT MATTER Int. Cl. ⁷ C07C 43/13, 43/188, 43/196, 41/26, 41/16, C09K 3/00 According to International Patent Classification (IPC) or to both national classification and IPC			
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) Int. Cl. ⁷ : C07C 43/13, 43/18-196, 41/26, 41/16, C09K 3/00 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) CAS ONLINE			
C. DOCUMENTS CONSIDERED TO BE RELEVANT			
Category*	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.	
A	JP, A, 2-290827 (Kao Corp.), Nov. 30, 1990 (Family: none)	1-6	
A	JP, A, 48-98012 (Unilever N.V.), Dec. 13, 1973 & BE, A, 795751 & NL, A, 7302675 & DE, A1, 2309256 & FR, AL, 2174104 & GB, A1, 1422272 & US, A, 4029759 & AT, A, 7301692 & CH, A, 578841 & CA, A, 1007108	1-3, 5	
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.			
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed		"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family	
Date of the Actual Completion of the International Search Jan. 18, 1994		Date of Mailing of the International Search Report Feb. 8, 1994	
Name and Mailing Address of the ISA/ Japanese Patent Office (ISA/JP)		Signature of Authorized Officer	4H 8619
		Telephone No.: 03-3581-1101 Extension 3445	